



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b>  <b>A61K 31/365, 31/19</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/44028</b>  <b>(43) International Publication Date:</b> 27 November 1997 (27.11.97)
<b>(21) International Application Number:</b> PCT/US97/08041  <b>(22) International Filing Date:</b> 13 May 1997 (13.05.97)  <b>(30) Priority Data:</b> 60/017,878                      17 May 1996 (17.05.96)                      US 9612063.9                      10 June 1996 (10.06.96)                      GB  <b>(71) Applicants (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> HANCOCK, Bruno [GB/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). WINTERS, Conrad [GB/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). GERTZ, Barry [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). EHRICH, Elliot [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> COMPOSITIONS FOR A ONCE A DAY TREATMENT OF CYCLOOXYGENASE-2 MEDIATED DISEASES  <b>(57) Abstract</b>  <p>This invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day administration, said composition comprising a cyclooxygenase-2 inhibiting compound characterized by high potency, a long half-life and a high degree of specificity for inhibiting cyclooxygenase-2 in preference to cyclooxygenase-1. Such a compound is exemplified 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone. In one aspect, this invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising 5 to 125 mgs of the above mentioned compound. The invention is also directed to a method of treating cyclooxygenase-2 mediated diseases comprising the once a day oral administration of 5 to 125 mgs of the above-mentioned compound. The invention is also directed to the use of the above-mentioned compound in the manufacture of a medicament containing 5 to 125 mgs of said compound for once a day administration for the treatment of cyclooxygenase-2 mediated diseases.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

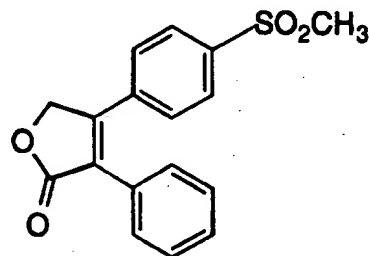
## TITLE OF THE INVENTION

### COMPOSITIONS FOR A ONCE A DAY TREATMENT OF CYCLOOXYGENASE-2 MEDIATED DISEASES

#### 5 BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions for the treatment of cyclooxygenase-2 mediated diseases, mehe use of a compound in the manufacture of a medicament.

10 In particular, this invention relates to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day administration, said composition comprising a cyclooxygenase-2 inhibiting characterized by high potency for the inhibition of cyclooxygenase-2, a long half-life and a high degree of specificity for inhibiting cyclooxygenase-2 in  
15 preference to cyclooxygenase-1. Such a compound is exemplified by 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,



20 Non-steroidal anti-inflammatory agents are normally administered 2 to 4 times daily. The relatively short half-life of most non-steroidal anti-inflammatory agents means that once a day administration is impractical and even twice a day administration is unusual. The relatively large doses needed to achieve once a day treatment of conventional non-steroidal anti-inflammatory agents would  
25 also lead to side effects so that there is a general understanding that once a day administration is unlikely to be achievable.

- 2 -

Surprisingly a compound has been identified which can be employed on a once a day basis and which will not produce an unacceptable level of side effects on such a regimen, and in particular will not cause an unacceptable level of gastric side effects.

5 US 5,474,995, issued December 12, 1995, WO 95/00501, published January 5, 1995 and WO 95/18799, published July 13, 1995, disclose 3,4-di-substituted furanones and derivatives thereof as potent, selective inhibitors of cyclooxygenase-2. We have found that 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone, possesses a surprising  
10 combination of attributes that make it possible to formulate and use the composition in a surprising manner. Not only is the compound potent, safe and effective at modest oral dosages of 5 to 125 mg of agent per day, but in addition this active agent possesses a half-life in humans of sufficient length that a single oral dose of 5 to 125 mg of agent per day  
15 will provide effective safe anti-inflammatory treatment over a 24 hour period. Such active agents are particularly useful in the treatment of chronic indications, including arthritis, pain, Alzheimer's disease and the like.

## 20 SUMMARY OF THE INVENTION

This invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising a cyclooxygenase-2 inhibiting compound  
25 characterized by high potency for the inhibition of cyclooxygenase-2, a long half-life and a high degree of specificity for inhibiting cyclooxygenase-2 in preference to cyclooxygenase-1. Such a compound is exemplified by 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone.

30 In one aspect, this invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said

- 3 -

composition comprising 5 to 125 mgs of the above mentioned compound.

The invention is also directed to a method of treating cyclooxygenase-2 mediated diseases comprising the once a day oral  
5 administration of 5 to 125 mgs of the above mentioned compound.

The invention is also directed to the use the above mentioned compound in the manufacture of a medicament containing 5 to 125 mgs of said compound for once a day administration for the treatment of cyclooxygenase-2 mediated diseases.

10

#### DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, this invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day  
15 administration, said composition comprising a cyclooxygenase-2 inhibitor characterized by high potency for the inhibition of cyclooxygenase-2, a long half-life and a high degree of specificity for inhibiting cyclooxygenase-2 in preference to cyclooxygenase-1.

In one genus, of this embodiment, this invention is directed  
20 to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising a cyclooxygenase-2 inhibiting compound characterized by.

(a) high potency for the inhibition of cyclooxygenase-2 as  
25 measured by the ability of a single therapeutic dose of said compound to provide relief from the post-operative pain accompanying the removal of two or three molars, said relief being statistically equal to or greater than that obtained with a single dose of 400 mg of ibuprofen;

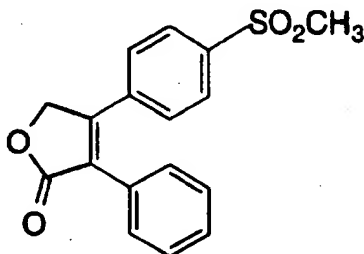
(b) a half-life of 9 or more hours, preferably 15 hours or  
30 more and more preferably 18 hours or more; and

(c) a high degree of specificity for inhibiting cyclooxygenase-2 in preference to cyclooxygenase-1 as measured by the

- 4 -

statistical failure of a therapeutic dose of said compound to inhibit the generation of serum thromboxane B2.

One such compound is 3-phenyl-4-(4-methylsulfonylphenyl)-2-(5H)-furanone,



5

As will be appreciated by those of skill in the art, this invention is directed only to compounds which act by inhibiting cyclooxygenase-2. Thus, the characterization requirements set out above cannot be said to be met unless the mode of action of the compound is as an inhibitor of cyclooxygenase-2. For example, a central nervous system agent may relieve pain with a potency equal to or greater than ibuprofen, yet not meet the requirements set out above, because it does not act on cyclooxygenase-2. See Inflamm. Res. 45:68-74 (1996) incorporated herein by reference, which discloses an (LPS)-challenge test for clinical identification and evaluation of cyclooxygenase-2 inhibition, and thromboxane B2 levels in the blood. Equivalent tests may also be used. Compounds of the instant invention are not hepatotoxic at therapeutic doses. Moreover, compounds of the instant invention demonstrate an ED30 in the rat paw edema assay of 0.4 mg/kg or less when measured as disclosed in WO 95/00501 and a selectivity for the inhibition of COX-2 over COX-1 of 50:1 or more measured as disclosed on WO 95/00501.

In one embodiment, this invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising a 5 to 125 mg of 3-phenyl-

25

- 5 -

4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone, and a pharmaceutical carrier therefor.

3-Phenyl-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone, its utility and methods of making them are disclosed in US 5,474,995, issued December 12, 1995, WO 95/00501, published January 5, 1995 and WO 95/18799, published July 13, 1995, which are hereby incorporated by reference.

As discussed in US 5,474,995 compounds, including 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone, are useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. It is also useful for the treatment of dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer Disease (ie Alzheimer's dementia).

The compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

By virtue of its high cyclooxygenase-2 (COX-2) inhibitory activity and/or its selectivity for inhibiting COX-2 over cyclooxygenase-1 (COX-1) the specified compound is also useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such NSAIDS may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of

- 6 -

gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems (including those relating to reduced or impaired platelet function); kidney disease (eg impaired renal function); those prior to  
5 surgery or taking anticoagulants; and those susceptible to NSAID induced asthma.

For the treatment of any of these cyclooxygenase mediated diseases the compound may be administered orally or by intravenous infusion.

10 As indicated above, pharmaceutical compositions for treating COX-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as  
15 tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. The compositions are intended for oral use and may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one  
20 or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the  
25 manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example,  
30 magnesium stearate, stearic acid or talc.

Other suitable formulations are set forth in U.S. Patent No. 5,474,995. However, in view of the unique set of properties possessed



- 7 -

by 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, including long half-life, low solubility, high potency, de minimis gastrointestinal (GI) side effects, we have found the following oral formulations to be of particular value:

5           Rapidisc® – In view of the above mentioned characteristics, 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone is particularly well suited for a rapid dissolving sublingual formulation. For example, due to the lack of GI side-effects, the agent need not be take with a large amount of water. Suitable Rapidisc® formulations and methods of  
10 making same are disclosed in US 4,305,502, US 4,371,516, US 4,470,202, US 4,758,598, US 4,754,597, US 5,046,618 and US 5,188,882, all of which are hereby incorporated by reference.

As mentioned in the Background section, we have found 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone to possess a  
15 surprising combination of attributes. Not only are these active agents potent safe and effective at modest oral dosages of 5 to 125 mg of agent per day, but in addition these active agents possess a half-life in humans of sufficient length that a single oral dose of 5 to 125 mg of active agent per day will provide effective safe anti-inflammatory treatment over a  
20 24 hour period. Such agents are particularly useful in the treatment of chronic indications, such as rheumatoid and osteo arthritis as well as Alzheimer's Disease.

Oral and intravenous dosage levels for agent 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone are of the order of from about  
25 5 to 125 per patient per day.

The amount of active agent that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans  
30 may contain from 5 to 125 mg of agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit

- 8 -

forms may typically contain 5, 10, 12.5, 20, 25, 50, 75, 100 or 125 mg of active agent.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination and the type and severity of the particular disease undergoing therapy. For many patients, a dosage range of 5 to 50 or 12.5 to 25 or 25 to 75 mg per day is preferred.

For long term therapy, such as in the treatment of chronic diseases including rheumatoid arthritis, osteoarthritis or Alzheimer disease, a dosage of 5 to 50 or 12.5 to 25 mg per day is preferred. More particularly, for the treatment of osteoarthritis, a dosage of 5, 10, 12.5, 25 or 50 mg per day is preferred, whereas for the treatment of rheumatoid arthritis, 10, 12.5, 25 or 50 mg per day is preferred. For the treatment of non-chronic indications such as headache or post-operative swelling and pain, 10, 12.5, 25 or 50 mg per day is preferred.

Accordingly, in one aspect the invention is directed to a unit dose oral form which comprises from 5 to 50 or 5 to 22.5 mg of the cyclooxygenase inhibitor, for example, 12.5 or 20 mg or 12.5 to 25.

In another aspect this invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition suitable for once a day oral administration, said composition comprising a 5 to 50 or 25 to 75 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, and a pharmaceutical carried therefor.

Within this aspect there is a first genus of compositions comprising 5 to 50 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

Within this aspect there is a second genus of compositions comprising 10 to 50 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

- 9 -

Within this genus there is a class of compositions comprising 5 to 22.5 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

5 Within this genus there is a class of compositions comprising 12.5 to 25 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

10 Within this genus there is a class of compositions comprising 5, 10, 12.5, 25 or 50 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

### EXAMPLE 1

#### Wet granulated tablet composition

15	Amount per tablet	Ingredient
	25 mg	COX-2 Inhibitor
	79.7 mg	Microcrystalline cellulose
	79.7 mg	Lactose monohydrate
20	6 mg	Hydroxypropyl cellulose
	8 mg	Croscarmellose sodium
	0.6 mg	Iron oxide
	1 mg	Magnesium stearate

25 Tablet dose strengths of between 5 and 125 mg can be accommodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

- 10 -

EXAMPLE 1aWet granulated tablet composition

5	Amount per tablet	Ingredient
	12.5 mg	COX-2 Inhibitor
	86 mg	Microcrystalline cellulose
	86 mg	Lactose monohydrate
10	6 mg	Hydroxypropyl cellulose
	8 mg	Croscarmellose sodium
	0.6 mg	Iron oxide
	1 mg	Magnesium stearate

15 EXAMPLE 1bWet granulated tablet composition

20	Amount per tablet	Ingredient
	10 mg	COX-2 Inhibitor
	87.2 mg	Microcrystalline cellulose
	87.2 mg	Lactose monohydrate
	6 mg	Hydroxypropyl cellulose
25	8 mg	Croscarmellose sodium
	0.6 mg	Iron oxide
	1 mg	Magnesium stearate

30 EXAMPLE 1cWet granulated tablet composition

35	Amount per tablet	Ingredient
	5 mg	COX-2 Inhibitor
	89.7 mg	Microcrystalline cellulose
	89.7 mg	Lactose monohydrate
	6 mg	Hydroxypropyl cellulose

- 11 -

8 mg	Croscarmellose sodium
0.6 mg	Iron oxide
1 mg	Magnesium stearate

5 **EXAMPLE 2**  
**Directly compressed tablet composition**

	<b>Amount per tablet</b>	<b>Ingredient</b>
10	25 mg	COX-2 Inhibitor
	106.9 mg	Microcrystalline cellulose
	106.9 mg	Lactose anhydrate
	7.5 mg	Croscarmellose sodium
	3.7 mg	Magnesium stearate

15 Tablet dose strengths of between 5 and 125 mg can be accommodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

20 **EXAMPLE 2a**

**Directly compressed tablet composition**

25	<b>Amount per tablet</b>	<b>Ingredient</b>
	12.5 mg	COX-2 Inhibitor
	113.2 mg	Microcrystalline cellulose
	113.2 mg	Lactose anhydrate
30	7.5 mg	Croscarmellose sodium
	3.7 mg	Magnesium stearate

**EXAMPLE 2b**

35 **Directly compressed tablet composition**

<b>Amount per tablet</b>	<b>Ingredient</b>
--------------------------	-------------------

- 12 -

	10 mg	COX-2 Inhibitor
	42.5 mg	Microcrystalline cellulose
	42.5 mg	Lactose anhydrate
	4 mg	Croscarmellose sodium
5	1 mg	Magnesium stearate

EXAMPLE 2cDirectly compressed tablet composition

10	<b>Amount per tablet</b>	<b>Ingredient</b>
	5 mg	COX-2 Inhibitor
	45 mg	Microcrystalline cellulose
15	45 mg	Lactose anhydrate
	4 mg	Croscarmellose sodium
	1 mg	Magnesium stearate

EXAMPLE 3

20 . Hard gelatin capsule composition

	<b>Amount per capsule</b>	<b>Ingredient</b>
25	25 mg	COX-2 Inhibitor
	37 mg	Microcrystalline cellulose
	37 mg	Lactose anhydrate
	1 mg	Magnesium stearate
	1 capsule	Hard gelatin capsule

30 Capsule dose strengths of between 1 and 50 mg can be accommodated by varying total fill weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

35

- 13 -

**EXAMPLE 4****Oral solution****5    Amount per 5 mL dose    Ingredient**

50 mg                      COX-2 Inhibitor  
to 5 mL with Polyethylene oxide 400

- 10    Solution dose strengths of between 1 and 50 mg/5mL can be accommodated by varying the ratio of the two ingredients.

**EXAMPLE 5****15    Oral suspension****Amount per 5 mL dose    Ingredient**

- 20                      101 mg                      COX-2 Inhibitor  
                         150 mg                      Polyvinylpyrrolidone  
                         2.5 mg                      Poly oxyethylene sorbitan monolaurate  
                         10 mg                      Benzoic acid  
                         to 5 mL with sorbitol solution (70%)

- 25    Suspension dose strengths of between 1 and 50 mg/5ml can be accommodated by varying the ratio of the first two ingredients.

**EXAMPLE 6****Intravenous infusion**

30

**Amount per 200mL dose    Ingredient**

- 1 mg                      COX-2 inhibitor  
                         0.2 mg                      Polyethylene oxide 400  
35                      1.8 mg                      Sodium chloride  
                         to 200mL                      Purified water

- 14 -

## STARTING MATERIALS

### PREPARATION 1

5    3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Step 1:    2-Bromo-1-(4-(methylsulfonyl)phenyl)ethanone

    A solution of 197 g of 4-(methylthio)acetophenone (ref: J. Am. Chem. Soc., 1952, 74, p. 5475) in 700 mL of MeOH and 3500 mL of CH<sub>2</sub>Cl<sub>2</sub> was added 881 g of MMPP over a period of 30 min. After 3  
10 h at r.t. the reaction mixture was filtered and the filtrate was washed with 2 L of saturated aqueous solution of NaHCO<sub>3</sub> and 1 L of brine. The aqueous phase was further extracted with 2 L of CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> concentrated to give 240 g of 4-(methylsulfonyl)acetophenone as a white solid.

15        To a cooled (-5 °C) solution of 174 g of 4-(methylsulfonyl)-acetophenone in 2.5 L of CHCl<sub>3</sub> was added 20 mg of AlCl<sub>3</sub>, followed by a solution of 40 mL of Br<sub>2</sub> in 300 mL CHCl<sub>3</sub>. The reaction mixture was then treated with 1.5 L of H<sub>2</sub>O and the CHCl<sub>3</sub> was separated. The aqueous layer was extracted with 1 L of EtOAc. The combined organic  
20 extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product was recrystallized from 50/50 EtOAc/hexane to give 210 g of the title compound as a white solid.

Step 2:    3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

25        To a solution of phenylacetic acid (27.4 g, 201 mmol) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (Step 1) (60 g, 216 mmol, 1.075 eq.) in acetonitrile (630 mL) at 25°C was added slowly Et<sub>3</sub>N (30.8 mL, 1.1 eq.). The mixture was stirred for 20 min. at r.t. and then cooled in an ice bath. DBU (60.1 mL, 3 eq.) was slowly  
30 added. After stirring for 20 min. in the ice bath, the reaction was complete and the mixture was acidified with 1N HCl (color changed from dark brown to yellow). Then 2.4 L of ice and H<sub>2</sub>O were added, the mixture was stirred for a few minutes, and the precipitate was



- 15 -

filtered and rinsed with H<sub>2</sub>O, giving 64 g of crude wet product. The solid was dissolved in 750 mL of CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub>, filtered and 300 g of silica gel was added to the filtrate. The solvent was evaporated to near dryness (silica gel a bit sticky), the residue was applied on top of a silica gel plug in a sintered glass funnel and eluted with 10% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, giving after evaporation of the solvent and swishing in EtOAc, 36.6 g (58%) of the title compound.

Analysis: Calculated for C<sub>17</sub>H<sub>14</sub>O<sub>4</sub>S: C, 64.95; H, 4.49; S, 10.20  
Found: C, 64.63; H, 4.65; S, 10.44

### PREPARATION 2

#### 3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Into a 20 mL glass ampule are added 1 g of 2-(4-(methylsulfonyl)phenyl)phenylacetylene (J.Am.Chem.Soc., 1971, 93, p. 2979), 20 mg of Rh<sub>4</sub>(CO)<sub>12</sub>, 1.5 g of Et<sub>3</sub>N, 10 mL of THF, and 1 mL of H<sub>2</sub>O under a nitrogen atmosphere, and the ampule is placed in a 100-mL stainless steel autoclave. The reaction system is flushed three times with CO then charged at r.t. to an initial CO pressure of 100 atm. The reaction is carried out at 100°C for 5 h. The solution is then diluted with 50 mL of benzene and washed with brine and 1N HCl. The benzene solution is dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The crude products are separated by column chromatography on silica gel, eluting with 2:1 EtOAc/hexane to give the title compound and its regioisomer.

### PREPARATION 3

#### 3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Step 1: 2-trimethylsilyloxy-4-(4-(methylthio)phenyl)-3,4-dihydrofuran

- 16 -

To a solution of 3.86 g (19 mmol) of 4-bromothioanisole in 90 mL of Et<sub>2</sub>O cooled at -78°C, is added 22 mL of a 1.7 M solution of t-BuLi in pentane (38 mmol) dropwise. The reaction mixture is stirred for 15 min at -78°C and 3.8 g of CuI is added and the reaction mixture is allowed to warm to -40°C over a period of 30 min. A solution of 1.7 g of 2(5*H*)-furanone in 10 mL of THF is added. After stirring for 1 h, 2 mL of freshly distilled TMSCl is added dropwise. The reaction mixture is then treated with 2 mL of Et<sub>3</sub>N and 50 mL of sat. NaHCO<sub>3</sub>, and extracted with 100 mL of Et<sub>2</sub>O. The Et<sub>2</sub>O layer is dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the crude title compound which is used for the next step without further purification.

Step 2: 4-(4-(Methylthio)phenyl)-2-(5*H*)-furanone

To a solution of 4 g of Pd(OAc)<sub>2</sub> in 100 mL of acetonitrile is added dropwise the crude product from Step 1 (5 g) under nitrogen at r.t. After 10 h at r.t., the mixture is concentrated under reduced pressure and the residue is purified by flash chromatography on silica gel eluted with 2:1 hexane/EtOAc to give the title compound.

Step 3: 3-Iodo-4-(4-(methylthio)phenyl)-2-(5*H*)-furanone

To a solution of 3 g of the product of Step 2 in 30 mL of pyridine is added 8.7 g of I<sub>2</sub>. The mixture is stirred for 24 h and then diluted with 200 mL of Et<sub>2</sub>O, washed with 100 mL of 5N HCl and 50 mL of 5N Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The Et<sub>2</sub>O layer is dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound.

Step 4: 3-(Phenyl)-4-(4-(methylthio)phenyl)-2-(5*H*)-furanone

A mixture of 4 g of the product of Step 3, 3.7 g of PhB(OH)<sub>2</sub>, 0.4 g of Ph<sub>3</sub>As, 0.4 g of PdCl<sub>2</sub>(PhCN)<sub>2</sub> in 100 mL of

- 17 -

- benzene and 15 mL of 2N NaOH is refluxed for 6 h. After cooling to r.t., Et<sub>2</sub>O (200 mL) is added to the reaction mixture and the mixture is washed with 100 mL of saturated NaHCO<sub>3</sub>. The organic layer is dried over MgSO<sub>4</sub> and concentrated. The residue is purified by flash chromatography on silica gel eluted with 4:1 hexane/EtOAc to give the title compound.

**Step 5:**     3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

- To a solution of 3 g of the product of Step 4 in 80 mL of 10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH is added 5.5 g of MMPP. The reaction mixture is stirred at r.t. for 2 h and then diluted with 100 mL of 1:1 hexane/EtOAc. After filtration and concentration, the residue is purified by flash chromatography eluted with 2:1 EtOAc/hexane to give the title product.

## ABBREVIATIONS

- |                   |                                      |
|-------------------|--------------------------------------|
| DBU               | = 1,8-diazabicyclo[5.4.0]undec-7-ene |
| Et <sub>3</sub> N | = triethylamine                      |
| MMPP              | = magnesium monoperoxyphthalate      |
| THF               | = tetrahydrofuran                    |
| TMSCl             | = trimethylsilyl chloride            |

- 18 -

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising 5 to 125 mg of a compound is 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.
2. A composition according to Claim 1 comprising 5, 10, 12.5 or 25 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.
3. A composition according to Claim 1 comprising 10 to 125 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.
4. A composition according to Claim 1 comprising 10 to 75 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.
5. A composition according to Claim 1 comprising 10, 25, or 50 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.
6. A composition according to Claim 1 comprising 25, 50 or 75 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.
7. A pharmaceutical composition according to Claim 1, 2, 3, 4, 5, or 6 further comprising
  - (a) Microcrystalline cellulose,
  - (b) Lactose monohydrate,
  - (c) Hydroxypropyl cellulose,
  - (d) Croscarmellose sodium,
  - (e) Iron oxide, and
  - (f) Magnesium stearate; or further comprising
    - (a) Microcrystalline cellulose,

- 19 -

- (b) Lactose anhydrate,
- (c) Croscarmellose sodium, and
- (d) Magnesium stearate; or further comprising

5 Polyethylene oxide 400; or further comprising

- (a) Sorbitol solution,
- (b) Polyvinylpyrrolidone,
- (c) Poly oxyethylene sorbitan monolaurate, and
- 10 (d) Benzoic acid.

8. A method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:  
15 administration orally once a day to a patient in need of such treatment 5 to 125 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

9. A method according to Claim 8 comprising:  
administration orally once a day to a patient in need of such treatment 5,  
20 10, 12.5 or 25 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

10. A method according to Claim 8 comprising:  
administration orally once a day to a patient in need of such treatment  
25 10 to 125 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

11. A method according to Claim 8 comprising:  
administration orally once a day to a patient in need of such treatment  
30 10 to 75 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

12. A method according to Claim 8 comprising:

- 20 -

administration orally once a day to a patient in need of such treatment  
10, 25 or 50 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-  
furanone.

5                   13. A method according to Claim 8 comprising:  
administration orally once a day to a patient in need of such treatment  
25, 50 or 75 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-  
furanone.

10                   14. A method of treating an inflammatory disease  
susceptible to treatment with a non-steroidal anti-inflammatory agent  
comprising:  
administration orally once a day to a patient in need of such treatment a  
composition according to Claim 7.

15                   15. A method according to Claim 9 for the treatment of  
non-chronic headache, pain or swelling.

20                   16. A method according to Claim 12 for the treatment of  
osteoarthritis.

17. A method according to Claim 13 for the treatment of  
rheumatoid arthritis.

25                   18. Use of 5 to 125 mg of 3-phenyl-4-(4-methyl-  
sulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day  
oral dosage form of a medicament for the treatment of an inflammatory  
disease susceptible to treatment with a non-steroidal anti-inflammatory  
agent.

30                   19. Use according to Claim 18 of 5, 10, 12.5 or 25 mg of  
3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the

- 21 -

manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

5                   20. Use according to Claim 18 of 10 to 125 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

10                   21. Use according to Claim 18 of 10 to 75 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

15                   22. Use according to Claim 18 of 10, 12.5, 25 or 50 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

20                   23. Use according to Claim 18 of 10, 12.5, 25 or 50 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of osteoarthritis.

25                   24. Use according to Claim 18 of 25, 50 or 75 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

- 22 -

25. Use according to Claim 18 of 25, 50 or 75 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of  
5 rheumatoid arthritis.

26. Use according to Claim 18 of 5, 10, 12.5 or 25 mg of 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the  
10 treatment of non-chronic headache, pain or swelling.

27. A pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day administration, said composition comprising a  
15 cyclooxygenase-2 inhibiting compound characterized by

(a) high potency for the inhibition of cyclooxygenase-2 as measured by the ability of a single therapeutic dose of said compound to provide relief from the post-operative pain accompanying the removal of two or three molars, said relief being statistically equal to or greater  
20 than that obtained with a single dose of 400 mg of ibuprofen;

(b) a half-life of 15 hours or more; and

(c) a high degree of specificity for inhibiting cyclooxygenase-2 in preference to cyclooxygenase-1 as measured by the statistical failure of a therapeutic dose of said compound to inhibit the  
25 generation of serum thromboxane B<sub>2</sub>.

28. A composition according to Claim 27 comprising 5, 10, 12.5 or 25 mg of said cyclooxygenase-2 inhibitor.

30 29. A composition according to Claim 27 comprising 10 to 125 mg of said cyclooxygenase-2 inhibitor.



- 23 -

30. A composition according to Claim 27 comprising 10 to 75 mg of said cyclooxygenase-2 inhibitor.

31. A composition according to Claim 27 comprising 10, 25, or 50 mg of said cyclooxygenase-2 inhibitor.

32. A composition according to Claim 27 comprising 25, 50 or 75 mg of said cyclooxygenase-2 inhibitor.

33. A pharmaceutical composition according to Claim 27, 28, 29, 30, 31, or 32 further comprising

- (a) Microcrystalline cellulose,
- (b) Lactose monohydrate,
- (c) Hydroxypropyl cellulose,
- (d) Croscarmellose sodium,
- (e) Iron oxide, and
- (f) Magnesium stearate; or further comprising

- (a) Microcrystalline cellulose,
- (b) Lactose anhydrate,
- (c) Croscarmellose sodium, and
- (d) Magnesium stearate; or further comprising

Polyethylene oxide 400; or further comprising

- (a) Sorbitol solution,
- (b) Polyvinylpyrrolidone,
- (c) Poly oxyethylene sorbitan monolaurate, and
- (d) Benzoic acid.

34. A unit dose oral form which comprises from 5 to 22.5 mg of the cyclooxygenase inhibitor characterized by

- (a) high potency for the inhibition of cyclooxygenase-2 as measured by the ability of a single therapeutic dose of said compound to provide relief from the post-operative pain accompanying the removal

- 24 -

of two or three molar, said relief being statistically equal to or greater than that obtained with a single dose of 400 mg of ibuprofen;

(b) a half-life of 15 hours or more; and

(c) a high degree of specificity for inhibiting

- 5 cyclooxygenase-2 in preference to cyclooxygenase-1 as measured by the statistical failure of a therapeutic dose of said compound to inhibit the generation of serum thromboxane B<sub>2</sub>.

- 10 35. A unit dosage form according to Claim 34 which comprises 12.5 or 20 mg of the cyclooxygenase-2 inhibitor.

36. A unit dosage form according to Claim 35 which comprises 3-phenyl-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/08041

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/365 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 18799 A (MERCK FROSST CANADA INC) 13 July 1995 cited in the application *cf. abstract, page 10, line 17 (item "y"), page 11, lines 1-13, page 12, 3rd para.*	1-17, 27-36
X	WO 95 00501 A (MERCK FROSST CANADA INC ;DUCHARME YVES (CA); GAUTHIER JACQUES YVES) 5 January 1995 cited in the application *cf. abstract, page 24, line 26 (item "y"), page 26, last para. bridging with page 27, first para. page 32, 2nd para. to the foot of the page* --- -/--	1-17, 27-36

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents; such combination being obvious to a person skilled in the art.
- \*A\* document member of the same patent family

Date of the actual completion of the international search

18 September 1997

Date of mailing of the international search report

02.10.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

Stoltner, A

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/08041

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 474 995 A (DUCARME YVES ET AL) 12  December 1995  *cf. abstract, col. 6, line 35 (item "y"),  col. 7, lines 31-64*  -----</p>	<p>1-17.  27-36</p>

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/08041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9518799 A	13-07-95	US 5474995 A	12-12-95
		AU 1269495 A	01-08-95
		AU 1913297 A	14-08-97
		AU 6197096 A	31-10-96
		AU 6967494 A	17-01-95
		BG 100247 A	28-06-96
		BG 100350 A	31-12-96
		BR 9406979 A	05-03-96
		CA 2163888 A	05-01-95
		CA 2176973 A	25-12-94
		CA 2176974 A	25-12-94
		CA 2180651 A	13-07-95
		WO 9500501 A	05-01-95
		CN 1125944 A	03-07-96
		CN 1143365 A	19-02-97
		CZ 9503146 A	15-05-96
		EP 0705254 A	10-04-96
		EP 0739340 A	30-10-96
		EP 0754687 A	22-01-97
		FI 956119 A	19-12-95
		FI 962800 A	06-09-96
		HR 940373 A	31-12-96
		HU 74070 A	28-10-96
		HU 74986 A	28-03-97
		JP 9500372 T	14-01-97
		NO 955256 A	23-02-96
		NO 960393 A	09-07-96
		PL 312196 A	01-04-96
		SK 150295 A	08-01-97
		US 5536752 A	16-07-96
		US 5550142 A	27-08-96
<hr/>			
WO 9500501 A	05-01-95	US 5474995 A	12-12-95
		AU 1913297 A	14-08-97
		AU 6197096 A	31-10-96
		AU 6967494 A	17-01-95
		BG 100247 A	28-06-96
		BR 9406979 A	05-03-96
		CA 2163888 A	05-01-95
		CA 2176973 A	25-12-94

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/08041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9500501 A		CA 2176974 A	25-12-94
		CN 1125944 A	03-07-96
		CZ 9503146 A	15-05-96
		EP 0705254 A	10-04-96
		EP 0754687 A	22-01-97
		FI 956119 A	19-12-95
		HR 940373 A	31-12-96
		HU 74070 A	28-10-96
		JP 9500372 T	14-01-97
		NO 955256 A	23-02-96
		PL 312196 A	01-04-96
		SK 150295 A	08-01-97
		US 5536752 A	16-07-96
		US 5550142 A	27-08-96
		ZA 9404501 A	13-03-95
		AU 1269495 A	01-08-95
		BG 100350 A	31-12-96
		CA 2180651 A	13-07-95
		WO 9518799 A	13-07-95
		CN 1143365 A	19-02-97
		EP 0739340 A	30-10-96
		FI 962800 A	06-09-96
		HU 74986 A	28-03-97
		NO 960393 A	09-07-96
-----			
US 5474995 A	12-12-95	AU 1269495 A	01-08-95
		AU 1913297 A	14-08-97
		AU 6197096 A	31-10-96
		AU 6967494 A	17-01-95
		BG 100247 A	28-06-96
		BG 100350 A	31-12-96
		BR 9406979 A	05-03-96
		CA 2163888 A	05-01-95
		CA 2176973 A	25-12-94
		CA 2176974 A	25-12-94
		CA 2180651 A	13-07-95
		WO 9500501 A	05-01-95
		WO 9518799 A	13-07-95
		CN 1125944 A	03-07-96
		CN 1143365 A	19-02-97

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/08041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5474995 A		CZ 9503146 A	15-05-96
		EP 0705254 A	10-04-96
		EP 0739340 A	30-10-96
		EP 0754687 A	22-01-97
		FI 956119 A	19-12-95
		FI 962800 A	06-09-96
		HR 940373 A	31-12-96
		HU 74070 A	28-10-96
		HU 74986 A	28-03-97
		JP 9500372 T	14-01-97
		NO 955256 A	23-02-96
		NO 960393 A	09-07-96
		PL 312196 A	01-04-96
		SK 150295 A	08-01-97
		US 5536752 A	16-07-96
		US 5550142 A	27-08-96
		ZA 9404501 A	13-03-95
-----			